REMARKS

Claims 15-29 are pending. Claims 28 and 29 are new. No new matter is added by this amendment.

Support for new claims 28 and 29 may be found in claims 15, 21, 22, and at page 8, lines 8-19. Applicants have also submitted herewith a second supplemental Information Disclosure Statement.

I. Specification

The specification has been corrected to reflect the duplication of the word "of" in line 2 (at page 1) of the paragraph entitled "Cross-Reference to Related Applications." This correction overcomes the objection to the specification.

II. 35 U.S.C. §103

Claims 1 - 27 have been rejected under 35 U.S.C. §103 as being unpatentable over Morris et al, U.S. Patent No. 5,516,781 or Mitchell et al, U.S. Patent No. 5,288,711, in view of Schuler et al, U.S. Patent No. 6,384,064, Somers et al, U.S. Patent No. 6,121,319, Applicants' statement on page 5, line 10 – page 6, line 22 of the specification, and "The Merck Manual of Diagnosis and Therapy."

Applicants respectfully traverse this rejection. Further, Applicants have not provided any remarks regarding claims 1-14, as these claimed were canceled in response to the previous Action.

In summary, there is no motivation in the art to combine the teachings of the document. In fact, the teachings of Mitchell (which requires a component not recited in the claims) and Somers (which contains no teaching of a rapamycin) would lead one of skill in the art away from such a combination and any expectation of success. However, even if combined, the cited combination fails to suggest the present invention.

The documents cited by the Examiner which teach the use of a rapamycin, *i.e.*, Morris, Mitchell, and Schuler, teach treatment of cellular proliferation (treatment of disorders associated with a hyperproliferative condition), which in some situations is

induced by a preexisting injury to a vascular cell wall. The combined teachings of these documents do not suggest that rapamycin could be useful in prevention or inhibition of lipid accumulation or disorders caused by lipid accumulation even in the absence of a preexisting hyperproliferative condition.

The following discussion addresses the three points raised on pages 4-6 of the Office Action by the Examiner:

(i) *The Examiner argues that one of skill in the art concerned with hyperproliferative vascular disease would have been aware of not only Morris or Mitchell, but of Schuler as well, which is relied upon for teaching treatment of hyperproliferative vascular diseases including atherosclerosis with rapamycin derivatives.*

The description to the treatment using rapamycin in Morris, Mitchell, and Schuler, are based on the anti-hyperproliferative effect of rapamycin following direct injury to the cell wall, but none of the cited documents assessed the ability of the compounds to prevent lipid deposition or accumulation by the direct effect on plasma lipids.

The accumulation of lipids in the walls of blood vessels is an important aspect of the atherosclerotic process, but the prior art does not teach or suggest the use of a rapamycin for the prevention of lipid deposition or accumulation in a vascular wall, or the treatment or prevention of conditions that are associated with such lipid deposition or accumulation.

The data in the present application demonstrates the effect of rapamycin on plasma lipids and supports the medical use as expressed in claim 1. Low levels of HDL are considered a risk factor for vascular disease; similarly, elevated triglyceride levels are considered a risk factor. Table 1 in the present application shows that treatment with rapamycin significantly increased levels of HDL cholesterol, while not significantly affecting levels of triglycerides. The Table also goes on to shows there is a dramatic three fold reduction in the level of aortic atherosclerosis. As the description points out the aortic atherosclerosis data is a well accepted model of human atherosclerosis.

Thus, in the present situation the prior art is concerned with the effect of a rapamycin on hyperproliferation following vascular cell damage caused by injury, whereas the experiments described in the present specification by the Applicants are concerned with the plasma lipid/triglyceride levels and aortic atherosclerosis of normal animals.

(ii) *The Examiner argues that Somers teaches the pharmaceutical agents of claim 21 was known to be useful in treating vascular diseases .*

It is noted that Somers contains no teaching related to a rapamycin. Nor does Somers provide any suggestion to combine any other pharmaceutical agents with a rapamycin.

Somers teaches a method of treatment utilizing monoesters of probucol, optionally in combination with other medications. This document does not teach or suggest the use of a rapamycin. Thus, the combined teaching in this document with the other cited documents does not supply the missing suggestion necessary to render the present invention obvious.

(iii) *The Examiner notes that Morris teaches that rapamycin can treat hyperproliferative vascular diseases, including atherosclerosis. The examiner further notes that Morris describes atherosclerotic lesions as including lipid laden "foam cells".*

Applicants respectfully draw the Examiner's attention to the fact that the same passage in Morris attributes this to restenosis produced by proliferation of cells following a breech of endothelial cell wall integrity.

Neither Morris nor Mitchell suggest the use of any rapamycin derivatives, much less the derivatives recited in the present invention. The combination of the secondary references with Morris or Mitchell fails to suggest the present invention. Further, Mitchell teaches away from the present invention, as it requires the presence of heparin, which is not an element of the claimed invention. Somers and Merck do not even discuss the use of a rapamycin.

However, even if the teachings of the documents relied upon are combined, their teachings are disparate and fail to supply the suggestion necessary to render the present invention obvious.

The examiner relies upon Merck for its general teachings relating to stroke or multiinfarct dementia.

Applicants respectfully submit that Merck fails to supply the suggestion missing from the combined teachings of the other documents.

In many cases, vascular cell damage can be caused by lipid accumulation. However, if lipid accumulation can be prevented, vascular cell damage and the formation of plaques can also be prevented. The prevention of the formation of these plaques is useful for prevention and treatment of disorders including stroke and multiinfarct dementia.

Thus, while the ability of a rapamycin to treat cellular hyperproliferation was described in certain of the references, prior to the present invention, the ability of rapamycin to prevent lipid accumulation was previously unrecognized. The combined teachings of the cited documents fail to provide this suggestion.

Reconsideration and withdrawal of these rejections are requested.

III. Double Patenting

Claim 22 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 and 9 of U.S. Patent No. 6,680,330, in view of Wright et al, cited above, and Mitchell et al, cited above.

Applicants respectfully traverse this rejection.

The combined teachings of Zhu, Wright and Mitchell fail to suggest the present invention.

The defects in Wright and Mitchell have been previously described. Zhu, Wright and Mitchell are focused on restenosis following injury to vascular wall injury. Zhu relates only to rapamycin dialdehyde. Wright teaches only localized delivery of rapamycin. Mitchell requires heparin, which is not an element of the present claims.

Further, Applicant asserts that the Examiner's remarks spanning pages 9 and 10 of the present Action are moot, as the pending claims do not recite "the treatment or inhibition of cardiovascular disease or the treatment of atherosclerosis in general."

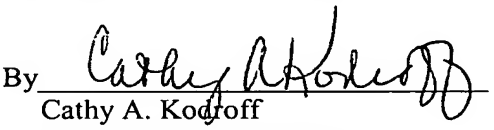
The combined teachings of the prior art do not suggest the ability of rapamycin to prevent lipid accumulation. Contrary to the Examiner's position, lipid deposition or accumulation is a process that may lead to vascular injury, which the documents relied upon are focused on restenosis following vascular injury. The treatment of restenosis is not present claimed.

Reconsideration and withdrawal of this rejection is requested.

The Director of the US Patent and Trademark Office is hereby authorized to charge any fee due to our Deposit Account, No. 08-3040.

Respectfully submitted,

HOWSON AND HOWSON
Attorneys for the Applicants

By 

Cathy A. Kodroff
Registration No. 33,980
Suite 210
501 Office Center Drive
Fort Washington, PA 19034
Phone: (215) 540-9210
Fax: (215) 540-5818